

Osteoarthritis and Cartilage



Brief report

The association between hip bone marrow lesions and bone mineral density: a cross-sectional and longitudinal population-based study



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SUMMARY

Objective: To describe the cross-sectional and longitudinal association between hip Bone marrow lesions (BMLs) and bone density.

Design: 198 subjects with a right hip MRI and dual-energy X-ray absorptiometry (DXA) scans conducted at two time points, approximately 2.6 years apart were included. MR images were used to assess hip BML presence and size (cm²) while DXA scans were used to determine bone mineral density (BMD) of the total hip, spine and femoral neck.

Results: Fifty-five subjects (28%) had either a femoral and/or acetabular BML. Cross-sectionally, acetabular BMLs were associated with 5–6% lower total hip [$P = 0.01$] and femoral neck BMD [$P < 0.001$]. Resolving acetabular BMLs were associated with a 1–2% increase in BMD at hip [$P = 0.05$] and femoral neck [$P = 0.01$]. In contrast, resolving femoral BMLs were associated with a 4% lower and incident femoral BMLs with 3% higher femoral neck BMD [$P = 0.04$, $P < 0.001$ resp.]. Finally, each 1 cm² change femoral BMLs was associated with increase in femoral neck BMD: +0.03 g/cm², 95% confidence intervals (CI): +0.00, +0.05, and enlarging acetabular BMLs was associated with decrease in hip: −0.01 g/cm², 95% CI: −0.03, −0.00 and femoral neck BMD: −0.01 g/cm², 95% CI: −0.03, −0.001.

Conclusion: Hip BMLs were associated with local BMD (hip and femoral neck) but not with spine BMD and these associations vary according to site. BML prevalence and change was low in this study, hence these findings need confirmation. However, we hypothesize that these associations represent a combination of changes related directly to the BML pathology or changes adjacent to the disease process.

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Introduction

Bone marrow lesions (BMLs) are a key feature of osteoarthritis (OA) and are associated with pain¹, cartilage defects, cartilage volume loss² and joint replacement¹. Similarly, BMLs of the hip are associated with hip pain and hip joint space narrowing³.

Bone density is usually higher in subjects with OA⁴ and its relationship with knee BMLs has been explored. Lo *et al.* documented an increased ratio of compartment specific local tibial bone mineral density (BMD) in association with knee BMLs⁵. We found a positive correlation between knee BMLs and subchondral bone density in a community based sample⁶. Furthermore, Hunter *et al.*, demonstrated an increased bone volume fraction but a decrease in tissue mineral density in cores of bone area affected by knee BMLs

in women awaiting knee replacement⁷. The increase in bone density may be due to ongoing remodeling of damaged trabeculae in areas where BMLs were located⁵.

Studies looking into the association between BMLs and bone density in joints other than the knee are limited⁸. Similar changes in bone density are seen in subjects with hip OA⁴, however the association between hip BMLs and BMD is yet to be examined. Hence, the aims of this study were to describe the cross-sectional and longitudinal relationship between hip BMLs and total hip, femoral neck and spine BMD.

Materials and methods

Subjects

The Tasmanian Older Adult Cohort (TASOAC) study is a population-based cohort and the study design has been extensively described in previous manuscripts^{1,2,6}. The hip protocol was added during the latter part of phase 2. In the current study a sample of 245

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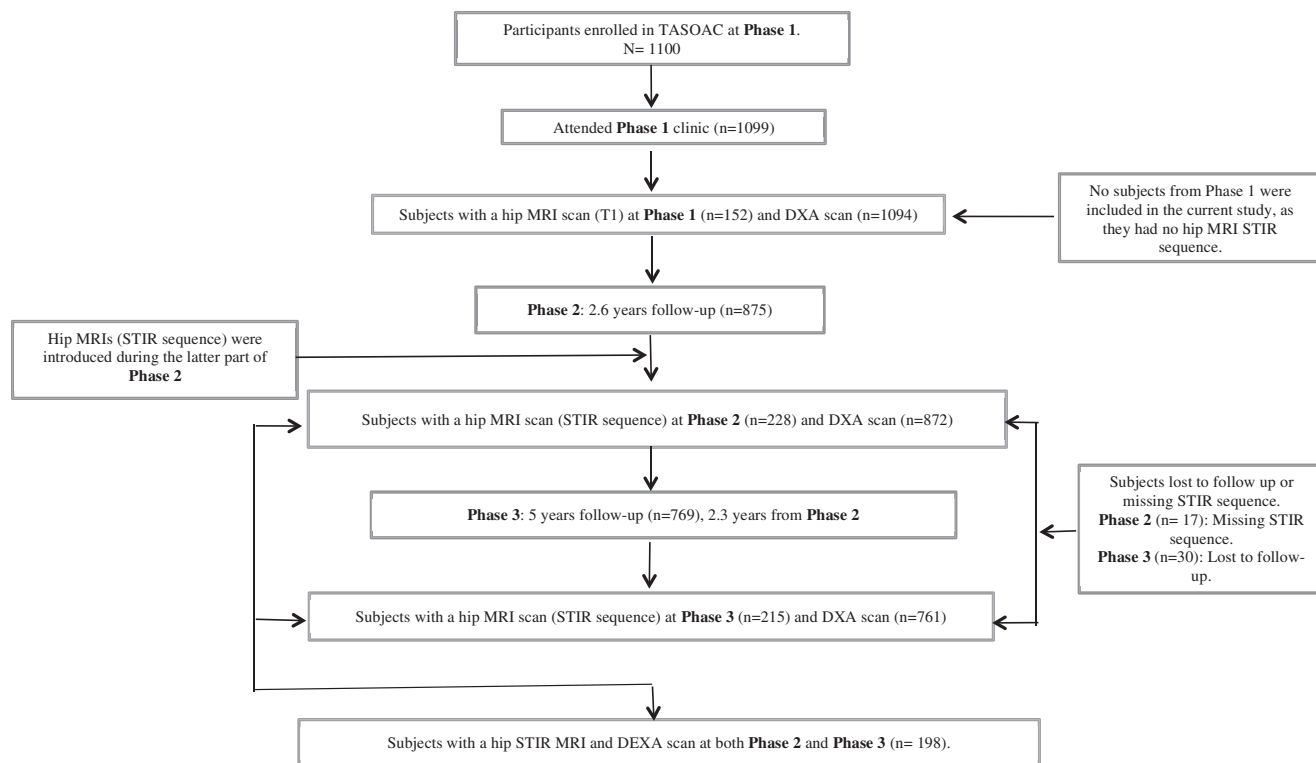


Fig. 1. Sample population inclusion chart.

consecutive participants with a Short T1 Inversion Recovery (STIR) MRI sequence at phase 2 and/or phase 3 were included (Fig. 1). Of these 245 participants, 30 participants were lost to follow-up at phase 3 and 17 participants had missing STIR sequences at phase 2 hence the total number of participants who had a hip STIR MRI scan at both phases was 198. This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and written informed consent was obtained.

Clinical and dual-energy X-ray absorptiometry (DXA) measurements

Height, weight and BMI were measured using standard protocols. BMD of the hip, femoral neck and spine at both phase 2 and phase 3 was assessed by DXA using a Hologic Delphi scanner as previously described⁶.

Magnetic resonance imaging

The right hip was imaged in the sagittal plane using a 1.5 T G.E signal whole-body magnetic resonance unit with a phased-array flex coil. The following image sequence was used: STIR-weighted fat saturation two-dimensional fast spin echo sequence; repetition time 4340 msec, echo time 28.4 msec; field of view 20 cm; 15 partitions and 512×512 pixel matrix. Sagittal images were obtained at slice thickness of 3.5 mm with an interslice gap of 1.5 mm.

Measurement of hip BMLs

For quantitative assessment of subchondral hip BMLs Osiri X software (University of Geneva, Geneva, Switzerland) was used. Hip BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum. One trained observer manually selected the MR slice with the largest BML and then scored the maximum area (cm^2) of all the identified lesions by manually drawing contours around their outer

edges (Fig. 2). The BML with the highest score was used if more than one lesion was present at the same site. Intra-observer repeatability was assessed and the intra-class correlation coefficient (ICC) of the hip, femoral and acetabular BMLs was 0.98, 0.96 and 0.99 respectively ($n = 25$), similar to the reproducibility of our knee quantitative BML measure¹.

Statistical analysis

Student's *t* tests and chi-squared tests were applied to determine the differences in means and proportions. The fit of all models were tested and all assumptions were fulfilled. Cross-sectional and longitudinal analyses were based on linear regression. Cross-sectionally, the relationship between hip BML presence or absence and BMD of the hip, femoral neck and spine was estimated by determining the mean difference in BMD of subjects with and

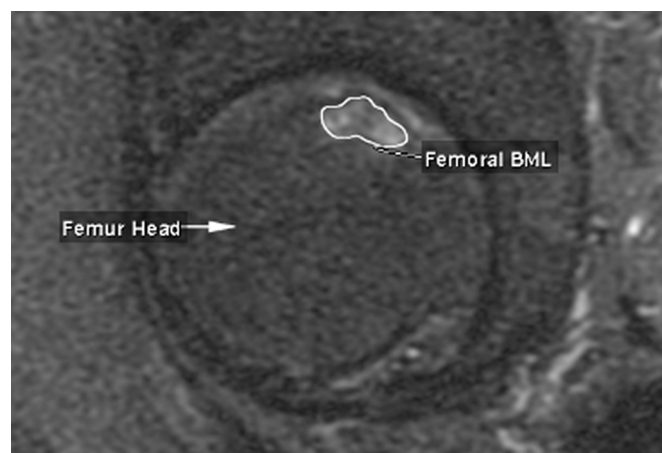


Fig. 2. Measurement of femoral BML.

without hip BMLs. These analyses were adjusted for age, sex, BMI and presence or absence of radiological hip OA (ROA), as adding covariates for these factors to the models changed the estimated coefficient of the study factor (BMLs) by more than 10%. For all cross-sectional analyses, data on subjects at phase 2 and phase 3 was combined and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance (Supplementary References 1–4). Lastly, the relationship between change in BML size and change in BMD of the hip, femoral neck and spine from baseline to follow-up for subjects with a BML at either time point was analyzed. All models were adjusted for age, sex and body mass index. All statistical tests were two sided and P values <0.05 were considered significant.

Results

Of the 198 subjects, 28% ($N = 55$) had a hip BML. Subjects with and without BMLs were similar in gender distribution (62% vs 54% male), mean age 64 years for both and mean [standard deviations (SD)] BMI [27.2 (4.40) vs 27.8 (4.61)]. BMD at the hip, spine and femoral neck was lower in subjects with any hip BML and the difference at the femoral neck [$P = 0.03$] was statistically significant. Lastly, acetabular BMLs [mean (SD): 0.74 (0.55)] were larger in comparison to femoral BMLs [mean (SD): 0.15 (0.41)].

Table I shows the cross-sectional relationship between hip BML presence and BMD at the hip, femoral neck and spine. The presence of acetabular BMLs was associated with lower BMD at the hip and femoral neck. Further, these associations persisted after adjustment for radiographic hip OA. BML size was not significantly associated with BMD but subjects with femoral BMLs had 12% lower femoral neck BMD as the difference in BMD per unit increase in femoral BML was -0.12 (95% CI $-0.24, +0.01$).

Table II presents the association between incident and resolving hip BMLs and change in BMD. Resolving femoral BMLs were associated with a decrease while incident femoral BMLs were associated with an increase in femoral neck BMD. Conversely, resolving acetabular BMLs were associated with an increase in hip and femoral neck BMD while incident acetabular BMLs were not associated with BMD at any site. Persistent hip BMLs were not associated with changes in bone density.

Lastly each 1 cm^2 change in acetabular BML size was associated with a decrease in total hip and femoral neck BMD: -0.01 , 95% CI: $-0.03, -0.004$ and -0.01 , 95% CI: $-0.03, -0.001$ respectively. Whereas per 1 cm^2 increase in femoral BML size was positively associated with increase in femoral neck BMD: $+0.03$, 95% CI: $+0.00, +0.05$.

Discussion

Hip BMLs were associated with local (total hip and femoral neck) BMD, but not distant BMD (spine). Furthermore, these associations vary according to site with femoral BMLs being associated with higher femoral neck BMD while acetabular BMLs are associated with lower hip and femoral neck BMD. The findings were consistent although not all were statistically significant.

The relationship between BMD and OA has been investigated⁴. Of these, only a few focus on the role of BMLs and bone density. Population-based studies in both participants with and without OA suggests that those with knee BMLs have higher local subchondral BMD^{5,6}. Further, knee BMLs are associated with increased bone density of the compartment where they are located. It is unclear whether this is due to BMLs having a local effect on bone or whether they are consequences of changes in underlying bone pathology. Demineralization of the bone under or adjacent to the BMLs could be explained by histological studies that suggest BMLs consist of elevated cytokines and angiogenic factors which leads to higher bone turnover locally, hence lower BMD^{7,9}.

At the hip, due to lack of data, the effects of BMLs on bone density or vice versa is currently unclear. One study reports osteoporosis in 4/8 resected femoral heads with hip BMLs but no correlation was found between this histopathological finding and hip BMLs³, however OA bone has been found to be hypo-mineralized with increased levels of water and organic materials¹⁰. In our study, femoral BMLs were associated with an increase in bone density. Longitudinally, resolving femoral BMLs were associated with decreasing and incident femoral BMLs were associated with increasing femoral neck BMD. Femoral BMLs would have been located in the similar or exact region in which total hip BMD was assessed. Conversely, acetabular BMLs that are adjacent but outside the region used to assess BMD, were associated with lower BMD. Cross-sectionally there was an estimated 5–6% decrease in total hip and femoral neck BMD. Longitudinally, bone density was higher in subjects with resolving acetabular BMLs, while a 1% reduction in BMD from baseline to follow-up was noted in subjects with enlarging acetabular BMLs. These findings demonstrate opposite associations for acetabular and femoral BMLs with BMD and should be regarded as hypothesis generating. For instance, overall increase in BMD and bone porosity in subjects with OA and BMLs has been documented^{5,7}. Additionally, femoral neck BMD in comparison to other locations at the hip is highest in early and severe radiographic hip OA⁴. It could be speculated that femoral BMLs located near the femoral neck may increase due to an increase in femoral neck BMD or because of changes in the subchondral bone due to increase in bone infiltrates¹⁰. In contrast, acetabular BMLs that are located away from the femoral neck and the subchondral bone associate

Table I
Cross-sectional relationship between presence of hip BMLs and bone density at the hip, femoral neck and spine

BML category	Total hip BMD (g/cm ²)			Femoral neck BMD (g/cm ²)			Spine BMD (g/cm ²)		
	N*	Mean (SD)	Adjusted mean difference (95% CI)†	N*	Mean (SD)	Adjusted mean difference (95% CI)†	N*	Mean (SD)	Adjusted mean difference (95% CI)†
Femoral BML									
No BML	412	0.97 (0.14)		412	0.77 (0.11)		414	1.02 (0.16)	
BML present	15	0.99 (0.13)	+0.01 (−0.07, +0.10)	15	0.80 (0.11)	+0.02 (−0.06, +0.17)	15	1.03 (0.11)	<0.01 (−0.08, +0.08)
Acetabular BML									
No BML	361	0.98 (0.14)		361	0.79 (0.11)		363	1.03 (0.15)	
BML present	66	0.93 (0.12)	−0.05 (−0.09, −0.01)	66	0.73 (0.08)	−0.06 (−0.09, −0.03)	66	1.00 (0.15)	−0.03 (−0.08, +0.01)

Dependent variable: BMD. Independent variable: presence or absence of BMLs. CI, confidence intervals.

Boldface indicates statistically significant results ($P < 0.05$).

* N: numbers shown are from measurements of 198 subjects at phase 2 & phase 3 and include repeated observation on the same subjects. Moreover, data for total hip and femoral neck BMD for one subject at phase 2 and 1 subject at phase 3 was missing.

† Data adjusted for age, sex, body mass index and ROA.

Table II

Longitudinal relationship between change in prevalence of hip BMLs and change in bone density of hip, femoral neck and spine

BML category	N*	Change in total hip BMD (g/cm ²)	Change in femoral neck BMD (g/cm ²)	Change in spine BMD (g/cm ²)
		Difference in mean (95% CI)†	Difference in mean (95% CI)†	Difference in mean (95% CI)†
Femoral BML				
No BMLs	175			
Resolved BML	2	−0.03 (−0.09, +0.03)	−0.04 (−0.09, −0.01)	−0.03 (−0.09, +0.03)
Incident BML	4	+0.02 (−0.00, +0.04)	+0.03 (+0.02, +0.04)	<0.01 (−0.02, +0.01)
Persistent BML	4	−0.01 (−0.04, +0.01)	<0.01 (−0.02, +0.03)	−0.03 (−0.06, −0.00)
Acetabular BML				
No BML	146			
Resolved BML	12	+0.02 (−0.00, +0.34)	+0.01 (+0.00, +0.03)	<0.01 (−0.02, +0.02)
Incident BML	10	<0.01 (−0.01, +0.23)	<0.01 (−0.01, +0.02)	<0.01 (−0.02, +0.01)
Persistent BML	19	<0.01 (−0.02, +0.01)	<0.01 (−0.02, +0.01)	−0.02 (−0.04, −0.00)

Dependent variable: change in BMD. Independent variable: change in prevalence of BMLs.

Boldface indicates statistically significant results ($P < 0.05$).

For these analyses, hip BMLs present at baseline and not at follow-up were categorized as resolved BMLs. Hip BMLs present at follow-up but not at baseline were categorized as incident BMLs. Hip BMLs present at both baseline and follow-up were categorized as persistent BMLs.

* Number of subjects in each category excluding participants with missing data at baseline or follow-up.

† Data adjusted for age, sex and body mass index.

with a bone undergoing demineralization. Hence, unlike the knee, hip BMLs located in two different compartments might represent bone areas undergoing different pathological changes leading to variations in the bone density adjacent to that joint. Nevertheless, these results might differ if we were able to measure material bone density.

It's unclear if BMLs are the cause or effect of secondary mechanisms modifying the bone. Hip BMLs, in this study, were associated with changes in local BMD perhaps, due to continuous bone remodeling and/or bone reabsorption in bone areas with BML. Studies have found elevated bone biochemical markers such as bone alkaline phosphate (ALP), osteocalcin (OC), and increase in angiogenesis factors such as vascular endothelial growth factor (VEGF), cysteine-rich angiogenic inducer 61 (CYR61), in bone samples with BMLs, suggesting increased bone turnover⁹. Moreover, BMLs may also reflect a paracrine effect of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 (IL-1) and leptin, which associate with pain¹¹, cartilage loss¹² and lower bone density in subjects with OA^{13,14}. Lastly, bone density may alter due to disuse of a painful joint mainly due to unloading which encourages reduction in bone formation or modeling¹⁵. Hence, both imbalances in the bone metabolism and disuse due to pain possibly cause changes in bone that encourage formation of BMLs.

Limitations

Bone density was measured using DXA, which provides an areal two-dimensional BMD measure; hence our apparent BMD findings might differ from material BMD findings. As BMD can be influenced by differences in bone size we adjusted for age, sex and BMI, which would largely compensate for any such differences. We were unable to vary the region of interest for our scans thus the region of interest where BMD was measured may include all, part or none of the hip BMLs depending on the location of the BML which may explain differing regional results. Longitudinal analyses were carried out with only a small number of hip BMLs, however the overall results were consistent. Hip BMLs were assessed by both presence and cross-sectional area, which might miss very small shallow or flat BMLs. However, our areal measure has excellent performance metrics in the knee¹.

Conclusions

Hip BMLs were associated with local BMD (hip and femoral neck) but not with spine BMD and these associations vary

according to site. BML prevalence and change was low in this study, hence these findings need confirmation. However, we hypothesize that these associations represent a combination of changes related directly to the BML pathology or changes adjacent to the disease process.

Declaration of authors' contributions

HA, DA, FC and GJ contributed to the conception and design of the study. HA, LB and GJ contributed in analyses of the data. HA extracted data from MRI images and prepared the first draft of the manuscript. All authors contributed in data interpretation, critical revision and final approval of the manuscript. HA assumes responsibility for the integrity and accuracy of the data.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.joca.2013.06.002>.

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